REMARKS

This submission is in response to the non-final Office Action electronically mailed on November 15, 2007. Claims 1, 2 and 4-23 were previously pending, claims 18 and 19 having been withdrawn by the Examiner. Accordingly, claims 1, 2, 4-17 and 20-23 are pending and at issue.

As correctly noted in the Office Action, claim 17 was not withdrawn by the Examiner. This claim was mistakenly identified as "withdrawn" in the claim listing of Applicant's August 27, 2007 response. Claim 17 is now identified as "original". Applicants thank the Examiner for her attention to this detail.

Claim 14 has been amended to advance prosecution in view of the Examiner's antecedent basis rejection and for no other reason related to patentability.

Applicants request reconsideration of this application in view of the amendments and remarks below.

Comments Regarding March 12, 2007 Interview

Applicants thank Examiner Mercier and Examiner Kishore for their time and cooperation during the March 12, 2007 interview with the undersigned and David Bernstein, General and IP Counsel for the assignee of the present application. During the interview, Applicants noted their respectful disagreement with the obviousness rejection due to, *inter alia*, the prior art's teaching that other distinct forms of morphine should be employed over the base monohydrate.

As suggested by Examiner Kishore, applicants have filed a divisional application with claims directed to a method *of treating pain* comprising administering a controlled release morphine medicament, wherein the medicament is administered transmucosally to a subject in need thereof and the medicament includes the limitations currently recited in claim 1 and 21 of the instant application. Based on the interview, this divisional application -- which has been assigned Application No. 12/049,893 -- is believed to be in condition for allowance.

Objections to the Specification

The Examiner has objected to the amendments to the specification made in Applicants' August 27, 2007 Response, arguing that:

> Applicant has submitted amendments to the specification, which are new matter. Applicant has presented amendments, which would change the release profile from first order to zero order kinetics

(Office Action, page 2, paragraph 2). Applicants respectfully disagree that new matter has been added, or that applicants have "changed" the release profile in any way. To the contrary, the release profile is as originally set forth in the figures and examples of the application as-filed: a substantially linear absorption rate. *See, e.g.,* page 16, lines 11-12 of the application as filed, noting the linear curves for formulations containing chitosan. Applicants are merely attempting to correctly reference such linear absorption as zero-order kinetics.

The MPEP and governing case law explains:

> An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction.

MPEP 2163.07 II., *citing*, *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971). Thus, the amendment is not new matter if a person of ordinary skill would understand that linear uptake is not first-order kinetics, but instead zero-order kinetics.

As disclosed, for example, in U.S. Patent No. 4,361,545, linear uptake is properly characterized as zero order kinetics:

> A plot of the first four data points of the Fig. 1 curve for the [slow release formulation] is shown in Fig. 2. ***The linear plot demonstrates the in vivo zero order uptake of the active ingredient.***

('545 patent, col. 15, ll. 9-13, attached as Exhibit A to the Response). *See also* U.S Patent No. 6,296,873, col. 3, ll. 51-56; U.S. Published Application No. 20030104062, paragraphs 39 and 51. After noting the substantially linear uptake, a person of ordinary skill would recognize that reference to first order kinetics was an obvious error and that zero-order kinetics is the proper correction.

In objecting to the attempted correction of the *description* of the linear uptake originally disclosed in the specification, the Examiner has not addressed why MPEP 2163.07 II does not apply. In the absence of such an explanation, applicants request that the objections to the specification be withdrawn.

Objection to Claim 6

The Examiner has objected to claim 6 under 37 CFR 1.75(c) as being of improper dependent form because it purportedly fails to limit the subject matter of the previous claim. Claim 6 recites purified morphine base monohydrate whereas claim 1 recites morphine base monohydrate. According to the Examiner:

> [S]ince the prior art disclose morphine to be used in pharmacuetical compositions, it is the examiners position that one of ordinary skill would use purified morphine

(Office Action, page 3, lines 1-2). 37 CFR 1.75(c), cited by the Examiner, refers to multiple dependent claims and is not relevant. 37 CFR 1.75(b) states that a dependent claim must specify a further limitation on the subject matter of the previous claim. Claim 6 specifies a further limitation: ***purified*** morphine base monohydrate. Claim 1 does not require that the morphine base monohydrate be purified. Applicants respectfully submit that claim 6 further limits claim 1 and thus satisfies 37 CFR 1.75. Teachings of the prior art and whether one of ordinary skill in the art would use purified morphine are irrelevant to this inquiry.

Rejections Under 35 USC § 112, second paragraph

Claims 1-2, 4-17, 20-23 stand rejected as indefinite.

The Examiner asserts that the terms "therapeutically effective" and "an effective amount" are unclear, and that it is unclear exactly how much is effective and what the desired effect actually is. (Claims 1 and 21 (as amended) recite "a therapeutically effective amount of morphine base monohydrate" and "an effective amount of a controlled release chitosan polymer".)

These rejections were addressed in applicants August 27, 2007 response. The Examiner has not responded to these arguments and is requested to do so. They are reproduced below for the Examiner's convenience.

A therapeutically effective amount of morphine base monohydrate is an amount that is effective for the purpose for which the morphine is administered, and can be determined by a person of ordinary skill in the art in view of, for example, the potency of the morphine base

monohydrate, the route of administration and the mechanical system used to administer the formulation (see page 9, lines 1-6 of the application as filed).

An effective amount of a controlled release chitosan polymer is also definite, and is understood by persons of ordinary skill in the art. It refers to an amount of chitosan polymer that produces a controlled increase in plasma levels of morphine (or plasma levels of morphine metabolites) during the absorption phase after nasal administration (see page 7, lines 8-10 of the application as filed). A controlled increase in plasma levels of morphine is a morphine dosage that provides substantially linear uptake (see page 7, lines 17-18 of the application as filed).

Because the terms "therapeutically effective" and "an effective amount" would be understood by a person of ordinary skill in the art, applicants request that the indefiniteness rejections be withdrawn.

The Examiner states that it is unclear what absorption rate is characterized by having "substantially linear absorption rates" and that applicant has not defined the parameters of substantially, nor provided any means for the Examiner to ascertain the meaning.

While the term "substantially linear" is a relative term, relative terminology is not necessarily indefinite. *See* MPEP §2173.05(b). For example, the Federal Circuit held that one of ordinary skill in the art would know what was meant by the term "substantially equal". *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819 (Fed. Cir. 1988); See also *In re Mattison*, 509 F.2d 563 (CCPA 1975) (term "to substantially increase the effeciency" deemed definite).

A person of ordinary skill would understand what was encompassed by the term "substantially linear" when read in view of the application as-filed. For example, Figure 1 demonstrates what would be a substantially linear absorption rate when 15 mg of morphine base

was administered with and without chitosan. The absorption curve shown with triangles (morphine base with chitosan) in Figure 1 is at least substantially linear whereas the absorption curve shown with circles (morphine base without chitosan) is not substantially linear. Similarly, the absorption curves shown in Figure 2 for the 7.5 mg, 15 mg and 30 mg nasal formulations are at least substantially linear whereas the curves for the IV and oral formulations are not. Applicants request that the indefinitenes rejection based on the term "substantially linear" be withdrawn.

The Examiner states that the term "purified" is unclear. The Examiner states that a specific purity is not defined by the claim. In response applicants note that breadth does not equate to indefinitness, and a specific purity need not be recited so long as the term "purified" itself is clear. See MPEP 2173.04. The term "purified" would be understood by persons of ordinary skill to refer to morphine base monohydrate that has been obtained from a less-pure form of morphine base monohydrate. As the Examiner suggests, pharmaceutical grade morphine base monohydrate is generally purified morphine base monohydrate.

The Examiner alleges that there is insufficient antecedent basis for the limitation "antimicrobial agent" in claim 14. Antecedent basis for the term "antimicrobial agent" is provided by claim 1, from which claims 14 indirectly depends. The Examiner has not responded to this argument. Nevertheless, to advance prosecution, claim 14 has been amended to recite "comprising an antimicrobial agent present at a concentration of. . .". Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

The claims have been rejected as obvious over U.S. Patent Nos. 5,629,011, 5,955,502, 6,433,040 and 6,387,917. Consistent with the Applicants' August 28, 2007 response, the following nomenclature will be used throughout this Response:

U.S. Patent No. 5,629,011: "Illum II";

U.S. Patent No. 5,955,502: "Hansen";

U.S. Patent No. 6,433,040: "Dellamary"; and

U.S. Patent No. 6,387,917: "Illum I".

A. The Claims Are Not Obvious Over Illum II

Claims 1-2, 4-8, 16-17 and 21-23 stand rejected as obvious over U.S. Patent No. 5,629,011 issued to Illum (hereafter "Illum II"). Illum II is said to disclose a composition for nasal administration of polar metabolites of morphine; and an absorption-promoting agent such as chitosan.

1. Illum II Teaches that Metabolites of Morphine are Distinct From and Superior to Morphine

Applicants note that the present invention provides a controlled release formulation of morphine base monohydrate that provides substantially linear absorption rates upon administration. This beneficial pharmacokinetic profile is achieved when the base monohydrate form of morphine is combined with chitosan at the specific ratios specified in applicants' claim 1.

Unlike the present invention, in which certain advantages are achieved using the claimed morphine base monohydrate, Illum II stresses that *polar metabolites* of morphine should

be used *in the place of morphine*, such as morphine-6-glucuronide (M6G) and morphine-3-glucuronice (M3G). While the Office Action suggests that such polar metabolites would have suggested morphine base monohydrate, this is not supported by the reference. For example, Illum II explicitly instructs:

> Opioid analgesics are metabolized in the body to a variety of compounds that are more polar than morphine itself, and this is what we mean by the term metabolite as used herein.

(Illum I, col. 2, lines 4-7). Illum II clearly instructs that opioid *metabolites* are distinguished from opioids themselves, citing the specific case of morphine to argue that morphine metabolites are clearly preferred from morphine itself because the metabolites of morphine are more polar.

The distinction is not just one of subtly different compounds. Rather, according to Illum II, polar metabolites of morphine, as well as salts of morphine, are not only distinct, but also *superior* to morphine because:

> Morphine-6-sulphate which differs from morphine itself by having an ionizable group of Carbon-6 at physiological pH has been shown to be a more potent analgesic than morphine following intracerebroventricular administration in mice.
>
> * * *
>
> Data have indicated that, for example, morphine-6-glucuronide and morphine-6-sulphate could be many times more active than morphine. (Col. 3, lines 3-6).

(Illum II, col. 2, lines 19-23 and col. 3, lines 3-6). Accordingly, a person of ordinary skill in the art, absent benefit of the present application, would have used the polar metabolites of morphine, such as morphine-6-sulfate over morphine itself because the prior art would have taught polar metabolites of morphine are stronger analgesics than morphine itself.

Although Illum II mentions linear kinetics twice -- once in connection with an HPLC assay (Illum II, col. 9, lines 23-32) and once in connection with assumptions for normalization of an AUC calculation for intravenous administration (Illum II, col. 9, lines 52-57) -- these references do not appear to relate to the claimed linear absorption rates of the current invention. However; even assuming for the sake of argument that Illum II has made a passing reference to the claimed linear absorption rates, the reference would still have failed to suggest the claimed invention, because it specifically teaches away from the particular chemical entity (morphine base monohydrate) claimed by the Applicant.

2. Morphine is Distinct From Morphine Base Monohydrate

The Office Action asserts that because Illum II discloses morphine (for the purpose of providing an inferior comparison to polar metabolites of morphine) the reference also teaches morphine base monohydrate. Specifically, the Action states:

> According to the Merck index, Morphine has a formula of $C_{17}H_{19}NO_3 \cdot H_2O$, which applicants claim on page 4 of the specification to be the formula of morphine base monohydrate. It is therefore, the position of the examiner that the prior art is teaching morphine base monohydrate

(Office Action, page 13, first paragraph) Applicants respectfully disagree.

Attached as Exhibit A to this Response is a copy of the listing for "morphine" in the 12th edition of the Merck Index (1996). Next to the word "morphine" is the formula $C_{17}H_{19}NO_3$. The molecular weight of morphine is listed as 285.34 and it is in the form of short, orthrohombic, columnar prisms from anisole.

The Merck index also lists, as a separate entry, the monohydrate form of morphine. The monohydrate form has distinct physical properties as compared to morphine. The formula of the *monohydrate* form of morphine is listed as $C_{17}H_{19}NO_3 \cdot H_2O$, (note the added water), which would correspond to a molecular weight of 303.36. The Merck index states that morphine monohydrate is in the form of "short, orthorhombic *sphenoidal* prisms" (needles) from methanol.

In addition to the monohydrate form of morphine, the Merck index also lists the acetate trihydrate, mucate, tartrate trihydrate and 6-methyl ether forms of morphine (heterocodeine). Each of these, like the base monohydrate, are distinct from morphine itself. If one were to assume that the word "morphine" teaches the base monohydrate form of morphine because of the Merck index's grouping, one would also have to assume that the acetate trihydrate, mucate, tartrate trihydrate and 6-methyl ether forms of morphine are all equivalent. This cannot be the case because the Merck index also teaches heterocodeine, which is six times more potent than morphine. Applicants respectfully submit that the assertion that morphine base monohydrate would have been suggested by polar metabolites of morphine or morphine itself is incorrect.

During the interview of March 12, 2008, Examiner Kishore suggested that the arguments presented above would serve to eliminate Illum II as an effective reference; however, he reserved the right to seek to identify other art for the intended purpose of Illum II.

In view of the above, the subject matter of Claims 1-2, 4-8, 16-17 and 21-23, would not have been shown or suggested by Illum II, and as such, Applicants request that this rejection be withdrawn.

B. The Claims Are Not Obvious Over Hansen

Claims 1-2, 4-12, 16-17 20-21 and 23 stand rejected as obvious over U.S. Patent No. 5,955,502 issued to Hansen (hereafter "Hansen"). The Examiner states that Hansen discloses the use of a fatty acid ester as bioadhesive substances and that the compositions may further include chitosan, morphine, antioxidants and antimicrobials.

Applicants note that chitosan is not a fatty acid ester; it is a polysaccharide. This is recognized in the specification, (see Hansen, col. 12, lines 59-64 and claims of Hansen). Chitosan is mentioned as an example of a possible component of an inert core for *oral* administration (see Hansen, col. 12, lines 55-64). Morphine (not morphine base monohydrate) is listed amongst a laundry list of active agents than spans almost an entire column of Hansen. In short, there is absolutely no reason that Hansen would lead one of ordinary skill in the art to the discovery that forms a basis for the present application: that combining morphine base monohydrate with chitosan in specific ratios provides substantially linear transmucosal uptake of morphine upon administration.

In view of the above, the subject matter of Claims 1-2, 4-12, 16-17 and 20-21, and 23, would not have been shown or suggested by Hansen, and as such, Applicants request that this rejection be withdrawn.

C. The Claims Are Not Obvious Over Dellamary

Claims 1-2, 4-17 and 20-21 stand rejected as obvious over U.S. Patent No. 6,433,040 issued to Dellamary (hereafter "Dellamary") The Examiner states that Dellamary discloses methods, systems and compositions comprising relatively stable dispersions of perforated microstructures in a suspension medium. The compositions are preferably administered via a liquid dose for topical administration to the lung and for systemic delivery via the lung.

Like Hansen, Dellamary lists morphine amongst a laundry list of active agents. Inclusion of chitosan is merely contemplated, but is not a focus of the compositions of Dellamary. Instead, Dellamary relies upon microstructures suspended in liquid fluorochemical. As Dellamary is directed to an entirely different formulation system it would not have lead one of ordinary skill in the art to the discovery that that combining morphine base monohydrate with chitosan in specific ratios provides substantially linear uptake of morphine upon transmucosal administration.

In view of the above, the subject matter of Claims 1-2, 4-17 and 20-21, would not have been taught or suggested by Dellamary, and as such, Applicants request that this rejection be withdrawn.

C. The Claims Are Not Obvious Over Ilum I

Claims 1, 2, 4-17 and 21-23 stand rejected as obvious over U.S. Patent No. 6,387,917 issued to Illum et al. (hereafter "Ilum I"). The Examiner states that Illum I discloses compositions having a methane sulphonate salt of morphine that are adapted for nasal administration. Chitosan is added in order to provide increased absorption of the drug. The

references state that the formulations are suitable for nasal, oral, buccal, rectal or vaginal administration.

The Examiner argues that Examples 2 and 3 disclose a solution comprising morphine base (monohydrate) and chitosan for intranasal administration. In response, Applicants have previously argued that one basis for patentability is that a specific ratio of morphine base monohydrate to chitosan polymer provides substantially linear absorption upon transmucosal administration. Illum I does not disclose or suggest this finding at least because it teaches converting the base monohydrate form of morphine, or alternatively, using the hydrochloric acid form of the drug. Illum I does not teach the use of unconverted morphine base monohydrate as claimed by the Applicants.

In response to these arguments, the Action states:

> The Examiner notes that applicant has employed the terminology comprising allowing for the inclusion/addition of any number of components regardless of their material effect on the other components . . . While the reference teaches the equimolar amounts of acid to the morphine base, a conjugate base would be present and equilibrium would be established. Therefore barring some showing to the contrary, it is the examiner's position that some morphine base monohydrate would still be present in the final product.

(Office Action, paragraph spanning pages 5-6).

In response, Applicants note that even given the presence of some residual amount of base monohydrate -- which is not admitted but merely posited for purposes of argument -- such residual amount does not establish a *prima facie* case of obviousness. It must be acknowledged that the express intention of Examples 2 is to *convert* the base monohydrate to a methane sulfonate salt. It must also be acknowledged that Illum I provides no suggestion that *any* form of morphine could yield substantially linear uptake. Given the express preference for

the methane sulphonate salt, and lack of teaching or suggestion regarding the kinetics of the morphine formulation upon administration, it is unclear how a residual amount of the base monohydrate would lead one of ordinary skill to the discovery that one could combine *specific* ratios of chitosan to the base monohydrate in order to prepare a composition that surprisingly yields substantially linear transmucosal uptake upon administration.

Given that the base monohydrate is used as an intermediate in Example 2 and not a final product, and that Illum I does not disclose or suggest that substantially linear uptake can be obtained using *any* morphine formulation, applicants respectfully submit that Illum I does not support a prima facie case of obviousness.

In view of the above, the subject matter of Claims 1, 2, 4-17 and 21-23, would not have been shown or suggested by Illum I, and as such, Applicants request that the rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be passed to allowance. If there are any other issues remaining which the Examiner believes could be resolved either through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below. Applicants believe no fee is due at this time. However, if any fees are required, the Commissioner is authorized to charge such fee to Deposit Account No. 02-4377.

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Respectfully submitted,

By _____
Jason C. Chumney
Registration No.: 54,781

Baker Botts L.L.P.
30 Rockefeller Plaza
44th Floor
New York, NY 10112-4498
(212) 408-2500
(212) 408-2501 (fax)

Attorneys/Agents For Applicant